Troponin Component of Cardiotonic Effects of Levosimendan on Isolated Myocardium from Patients with Chronic Heart Failure

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Experiments on isolated myocardial preparations from patients with coronary heart disease showed that inotropic effects of levosimendan in a dose of 0.73 μmol/liter were primarily due to activation of cAMP-dependent systems of regulation of cell metabolism. Increased affinity of troponin C for Ca^{2+} impaired muscle relaxation in patients with chronic heart failure.

Key Words: *levosimendan; cardiotonic action; epinephrine*

Cardiotonic effects of drugs are associated with their action on various stages [3] of cell Ca^{2+} homeostasis. A new preparation levosimendan (Orion) possesses a considerable cardiotonic ability [5], inhibits cAMP-specific phosphodiesterase [4,5], causes recombination of troponin C and, therefore, increases its affinity for Ca^{2+} [7]. Adenylate cyclase is activated by β-adrenoceptor agonists. Here we compared the effects of levosimendan and β-adrenoceptor agonist epinephrine on the contractile activity of heart samples from patients with coronary heart disease (CHD).

MATERIALS AND METHODS

Trabeculae isolated from the right auricle of 6 patients (mean age 53 years) with chronic CHD (functional class III NYHA) during coronary bypass surgery were studied. These patients were examined and operated at the Department of Cardiovascular Surgery (Institute of Cardiology). Isolation of muscle preparations and their perfusion were performed as described elsewhere [1,2]. After adaptation, muscles were perfused with a solution containing 0.05 μmol/liter epinephrine to a maximum inotropic response. Perfusion with the epinephrine-free solution was resumed until recovery of the initial parameters of the contraction-relaxation cycle. The muscles were perfused with a solution containing 0.73 μmol/liter levosimendan and treated again with 0.05 mmol/liter epinephrine. Contractile activity of muscles was determined under isometric conditions. The curve of muscle tension and its first derivative were recorded. The amplitude of muscle tension and the rate of its increase or decrease were evaluated. The results were analyzed by Wilcoxon test [7].

RESULTS

Perfusion of isolated myocardial strips from CHD patients with a solution containing 0.05 μmol/liter epinephrine was accompanied by an increase in their contractile activity (Fig. 1). Single contraction observed against the background of epinephrine inotropic effects was characterized by a 40% increase in the amplitude of muscle tension and a 50% rise in the rate of muscle relaxation. Predominant acceleration of cardiac muscle relaxation in response to β-adrenoceptor agonists is a typical reaction of the contraction-relaxation cycle [3,8].

Perfusion of myocardial samples from CHD patients with physiological saline containing 0.73 μmol/liter levosimendan induced inotropic effects (Fig. 2). Levosimendan applied in this dose increased the contractile activity, but its cardiotonic action was gradual and delayed (by contrast to effects of epinephrine). The maximum cardiac muscle response to levosimen-

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dan developed over 6 min. It should be emphasized that under the effect of levosimendan, the rise in muscle tension and the rates of its increase and decrease were smooth and similar (70% of initial values). Epinephrine applied against the background of levosimendan did not potentiate the contractile response (Fig. 2). The amplitude of muscle tension curve and the maximum of its first derivative increased by 9% and 7%, respectively. The maximum of derivative that characterizes relaxation did not change.

The inotropic action of levosimendan and the absence of cardiotonic effects of epinephrine applied against the background of this agent confirm the fact that levosimendan in doses above 0.3 μmol/liter elevates cell content of cAMP due to inhibition phosphodiesterases [4,5]. Levosimendan induces practically similar changes in contraction and relaxation and, therefore, its effects are not only due to activation of cAMP-dependent Ca^{2+}-transporting systems in cardiomyocytes. This is confirmed by the fact that epinephrine applied against the background of levosimendan did not accelerate muscle relaxation, while epinephrine alone increased this parameter by 50%. Such results are probably due to increased affinity of troponin C for Ca^{2+} induced by levosimendan [7].

The data suggest that levosimendan should be used for the therapy of patients with CHD in doses of below 0.7 μmol/liter. Higher doses of this preparation induce cardiotonic effects but aggravate disturbances of cardiac diastolic functions.

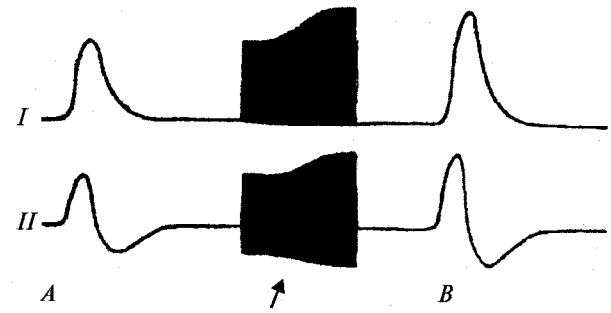

Fig. 1. Muscle tension (*I*) and its first derivative (*II*) after perfusion of myocardial preparation of CHD patients with epinephrine (*B*). Here and in Fig. 2: *A*, initial curves; arrows, application of epinephrine.

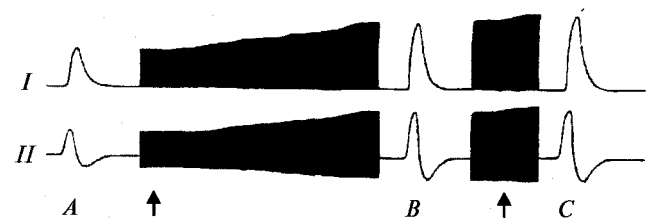

Fig. 2. Muscle tension (*I*) and its first derivative (*II*) after perfusion of myocardial preparation of CHD patients with levosimendan (*B*) and epinephrine (*C*).

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